REMARKS

Status of the Claims

Claims 1-44 were withdrawn from consideration and are now canceled. Claims 45-82 are pending. Claims 45-67 and 70-82 stand rejected under 35 U.S.C. §112, first paragraph as allegedly lacking enablement. Claims 51, 52, 59, 60, 63, and 77-82 stand rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite. Claims 45-48, 54-59, 61-65, 70, 71, and 72 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Gaster *et al.*, U.S. Patent No. 6,235,758. Claims 45-57 stand rejected under the judicially created obviousness-type double patenting as allegedly obvious over claims 46-67 of McNaughton-Smith *et al.*, U.S. Patent No. 6,593,349. Claims 45-82 stand rejected under the judicially created obviousness-type double patenting as allegedly obvious over claims 46-67 of McNaughton-Smith *et al.*, U.S. Patent No. 6,593,349, further in view of Gaster *et al.*, U.S. Patent No. 6,235,758. Claims 45-82 also stand rejected under the judicially created obviousness-type double patenting as allegedly obvious over claim 22 of US Patent 6,495,550 and claims 30-59 of US Patent 6,737,422. These rejections are addressed in the amendment filed on February 24, 2005.

The Invention

Applicants have demonstrated for the first time that openers of KCNQ potassium channels alleviate anxiety. The mechanism for treating anxiety by opening KCNQ potassium channels was previously unknown. Applicants have demonstrated the efficacy of this discovery using an *in vivo* experimental procedure routinely used by the pharmaceutical industry to screen for and identify drugs effective for the treatment of generalized anxiety disorder. The present application therefore provides not only a mechanism for treating anxiety disorders, but also a large number of structurally diverse compounds that open KCNQ potassium channels as well as assays for identifying compounds that open KCNQ potassium channels and reduce anxiety.

Rejections under 35 U.S.C. §103(a)

Applicants herein submit a signed expert declaration of Dr. Alan Wickenden under 37 C.F.R. § 1.132, which explains why one of skill in the art would find that Gaster fails to inherently teach or suggest that KCNQ potassium channel opening compounds can be used to treat anxiety.

The signed declaration and this supplemental amendment also clarify the following unintentional inaccuracies in the amendment and unsigned declaration filed on February 24, 2005. Gaster refers both to $5HT_{2B}$ and $5HT_{2C}$ receptors and their antagonists. This supplemental amendment is meant to correct quotes taken from the Gaster patent and to clarify that Applicants intended to refer to both $5HT_{2B}$ and $5HT_{2C}$ receptors and their antagonists, as discussed in Gaster.

1. Gaster asserts, but does not show experimentally, that "certain compounds of the invention exhibit $5HT_{2c}$ antagonist activity." See Gaster, column 1, lines 20-21. [not $5HT_{2B}$ as stated in the amendment and unsigned declaration].

2. Applicants acknowledge Gaster's statement that $5HT_{2B/2C}$ antagonists "are believed to be of potential use in the treatment of CNS disorders, such as anxiety . . . ." See Gaster, column 1, lines 21-23. [not $5HT_{2B}$ as stated in the amendment and unsigned declaration].

3. The Examiner has provided no basis or reasoning to support the assertion that a compound that reduces anxiety by antagonizing $5HT_{2B/2C}$ receptors necessarily increases ion flow through KCNQ potassium channels. [not $5HT_{2B}$ as stated in the amendment and unsigned declaration].

4. $5HT_{2B/2C}$ receptor antagonism is the only reported activity for these aryl carbamoyl compounds. One skilled in the art would immediately recognize that $5HT_{2B/2C}$ receptors radically differ in structure and function from KCNQ potassium channels. Therefore, there is no reason for one of skilled in the art to conclude, *a priori*, that the $5HT_{2B/2C}$ receptor

antagonists disclosed by Gaster would function to open KCNQ channels. [not $5HT_{2C}$ as stated in the amendment and unsigned declaration].

5. $5HT_{2B/2C}$ receptors belong to the class A or rhodopsin-like G-protein-coupled receptors (GPCRs), a seven-transmembrane domain protein family. In response to chemical or physical external stimuli, GPCRs undergo a conformational change directly leading to the activation of heterotrimeric G-proteins and other intracellular signaling mediators. By contrast, KCNQ channels do ***not*** belong to the GPCR family. Rather, KCNQ channels are composed of KCNQ subunits that are members of the Kv superfamily of potassium channel monomers. The KCNQ subunits form pores, allowing ions to pass in a voltage dependent manner, which does not directly lead to activation of heterotrimeric G-proteins. Because of the divergent structure and function of $5HT_{2B/2C}$ receptors and KCNQ channels, there is no reason to expect a $5HT_{2B/2C}$ receptor antagonist to increase ion flow through a KCNQ potassium channel. [not $5HT_{2C}$ as stated in the amendment and unsigned declaration]

6. Because one of skill in the art would have no reasonable expectation of successfully using the $5HT_{2B/2C}$ receptor antagonists of Gaster to treat anxiety by increasing ion flow through KCNQ potassium channels, Applicants respectfully request withdrawal of the rejection. [not $5HT_{2C}$ as stated in the amendment and unsigned declaration].

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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